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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/039,383	12/17/2001	Hsien-Jue Chu	AM100249	3951

25291 7590 09/07/2005

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EXAMINER

DEVI, SARVAMANGALA J N

ART UNIT PAPER NUMBER

1645

DATE MAILED: 09/07/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/039,383

Applicant(s)

CHU ET AL.

Examiner

S. Devi, Ph.D.

Art Unit

1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 06 April 2005.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 10-12 and 14-17 ~~is~~ are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 10-12 and 14-17 ~~is~~ are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- ☒ Notice of References Cited (PTO-892)
- ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____
- ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- ☐ Notice of Informal Patent Application (PTO-152)
- ☐ Other: _____

RESPONSE TO APPLICANTS' AMENDMENT

Applicants' Amendment

- 1) Acknowledgment is made of Applicants' amendment filed 04/06/05 in response to the non-final Office Action mailed 01/06/05.

Status of Claims

- 2) Claim 13 has been canceled via the amendment filed 04/06/05.
Claims 10, 11, 15 and 17 have been amended via this Examiner's amendment.
Claims 10-12 and 14-17 are pending and are under examination.

Prior Citation of Title 35 Sections

- 3) The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action.

Prior Citation of References

- 4) The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record.

Rejection(s) Moot

- 5) The rejection of claim 13 made in paragraph 18 of the Office Action mailed 01/06/05 under 35 U.S.C § 103(a) as being unpatentable over Petersen *et al.* (WO 92/03157) and Byars *et al.* (*Vaccine* 5: 223-228, 1987) in view of Liem *et al.* (US 20020114817, filed 09/29/1999), is moot in light of Applicants' cancellation of the claim.

Rejection(s) Withdrawn

- 6) The rejection of claims 10, 12 and 14-16 made in paragraph 18 of the Office Action mailed 01/06/05 under 35 U.S.C § 103(a) as being unpatentable over Petersen *et al.* (WO 92/03157) and Byars *et al.* (*Vaccine* 5: 223-228, 1987) in view of Liem *et al.* (US 20020114817, filed 09/29/1999), is withdrawn. A modified rejection is set forth below.
- 7) The rejection of claim 17 made in paragraph 19 of the Office Action mailed 01/06/05

under 35 U.S.C § 103(a) as being unpatentable over Petersen *et al.* (WO 92/03157) as modified by Byars *et al.* (*Vaccine* 5: 223-228, 1987) and Liem *et al.* (US 20020114817, filed 09/29/1999) as applied to claim 10 above, and further in view of Burkhardt *et al.* (US 6,342,231, filed 07/01/1998) and Potter *et al.* (US 5,534,256), is withdrawn. A modified rejection is set forth below.

Response to Applicants' Arguments

8) Applicant's arguments with respect to the art rejection of claim 17 have been considered but are moot in view of the withdrawal of, or the modified ground(s) of rejection.

With regard to the art rejection of claims 10, 12 and 14-16 made in paragraph 18 of the Office Action mailed 01/06/05 under 35 U.S.C § 103(a) as being unpatentable over Petersen *et al.* (WO 92/03157) and Byars *et al.* (*Vaccine* 5: 223-228, 1987) in view of Liem *et al.* (US 20020114817, filed 09/29/1999), Applicants submit the following arguments. To establish a *prima facie* case of obviousness, the guidelines of M.P.E.P. 706.02(j) and case law provide three basic criteria: (1) There must be some suggestion or motivation to modify the reference or to combine the reference teachings; (2) There must be a reasonable expectation of success; and (3) The combined references must teach or suggest all claim limitations. A *prima facie* case of obviousness can be rebutted by evidence of results that are unexpected and significant, i.e., the results are greater than those that would have been expected from the art to an unobvious extent and the results are of a significant, practical advantage. In the case at hand, the working examples demonstrate that the method of the present invention provides beneficial and unexpected results over those seen in the art. By way of background, it is explained that there has been an art-recognized problem in the administration of *Mycoplasma hyopneumoniae* bacterin in that young animals had to be handled twice or too often in order to get sufficient immunity against disease. Attempts have been made to overcome that problem and reduce the number of times that the young animals need vaccination. Fort Dodge Animal Health (FDAH) produces Suvaxyn RespiFend MH; that contains CARBOPOL (poly acrylic acid polymers) as an adjuvant, is recommended for semiannual revaccination but, undesirably, the vaccination schedule requires an initial two-dose vaccination, first shot for one-week old pigs, and a second booster shot two to three weeks after the primary vaccination. The two-dose vaccine has the obvious disadvantage of requiring a second handling of the young animals in

order to provide full protection against disease (see discussion in the Background of the Invention on page 2, lines 5-12 of the specification). Another commercially available product Ingelvac *M. hyo* manufactured by Boehringer Ingelheim, that contains an Impran water-in-oil emulsion, is effective through one dose but only lasts 120 days. The pigs must be revaccinated every four months. Example 3 on pages 12-19 of the specification shows that the new one-dose vaccination of the unique formulation of the present invention evidenced at least four months duration of immunity in pigs similar to the activity of Ingelvac *M. hyo*. Surprisingly, Example 4 on pages 20-25 of the specification demonstrates that the novel vaccine of this invention and the claimed method of using it provide superior, long-term immunity to a full six months after the single dose administration. The enhanced potency of the claimed formulation, currently marketed under the Tradename Suvaxyn MH-One, is an improvement over the earlier two-shot formulation (Suvaxyn RespiFend MH) that did not contain the claim-recited mixture of metabolizable oil and a polyoxyethylene-polypropylene block copolymer. The present invention solves the art-recognized problem and unexpectedly gives a new and improved method in which the animals are immunized by a single vaccination that provides exceptional six-month immunity against mycoplasmal pneumonia disease without the booster shot. Quite advantageously, the new method for the prevention or amelioration of disease caused by *Mycoplasma hyopneumoniae* utilizes the claim-recited adjuvant formulation to significantly enhance the immunogenicity of the bacterin and elicit excellent protective immunity for 182 days (label claim) after a single dose of the vaccine. By alleviating handling stress, reducing vaccination time, and decreasing labor time, the one-dose vaccination and long-acting immunity protection are very beneficial to the animal handlers and the animals themselves.

Examining what the collective art fairly teaches to the ordinary practitioner, it is clear that the practitioner would not arrive at the claimed invention. The art fails to provide any suggestion or motivation of the desirability of combining the references and doing what the inventors have done. The practitioner would find real distinction between the claimed method and the cited references. The PCT application corresponds to U.S. Patent No. 5,565,205 that is displayed on the vial labels of the *Mycoplasma Hyopneumoniae* Bacterin injectable product marketed as Suvaxyn RespiFend MH by FDAH. Petersen *et al.* are directly connected with the injectable product on the market in which

the method of vaccination mandates that a second dose follow two to three weeks after the first dose in order to achieve effective vaccination of the pigs.

The working examples of Petersen *et al.* show that the treatment groups received second injections two weeks after the first injections, and the standard two-shot vaccination method provided protection to 4 months of age (see Example 3 on pages 34-36 of the reference). While the reference implies that one dose of the bacterin can be injected into swine (page 12, lines 12-16), one of ordinary skill in the art would understand that the effects will not be long lasting and will not give meaningful protection. To achieve efficacy and long-term immunity up to four months, it is taught in the examples of Petersen *et al.* that the bacterin must be administered twice to the pig. Petersen *et al.* differ from the instant invention in not describing a mixture of metabolizable oil and a polyoxyethylene-polypropylene block copolymer. Contrary to the Office's opinion, Byars *et al.* do not teach or suggest that such a mixture should be combined with the *Mycoplasma hyopneumoniae* bacterin of Petersen *et al.* Byars *et al.* actually teach away from the claimed invention. In the 'Introduction' on the first page of the reference, Byars *et al.* state that for some bacterial and viral diseases, the humoral responses provide adequate protection. For relatively weak antigens such as a number of viruses, parasites, fungi and tumors, cell-mediated immunity is the major protective mechanism of the host response. While the only antigen tested for the article was egg albumin, the 'Discussion' on page 226 of the reference states that the authors' adjuvant formulation has been used with a pre-s protein of the hepatitis B virus, the formalin- inactivated feline leukemia virus and the simian type D retrovirus vaccines. There are no specific examples of any bacterin, or an implication that the *Mycoplasma hyopneumoniae* bacterin might be a weak antigen and require their adjuvant formulation. One of ordinary skill in the art would conclude based on the express teachings of Byars *et al.* that there would be no reason to combine the *Mycoplasma hyopneumoniae* bacterin with the adjuvant formulation of Byars *et al.* and no benefit would be expected from such a combination. Furthermore, the authors describe their method of 'Immunization' of the various preparations such that each guinea pig received egg albumin and MDP in the 'primary immunization' and, at 4 weeks of age; a 'boost' of antigen without MDP was given. There is no teaching or inference that the immunization process should omit the second booster shot. Plus, the studies only went to 49 days and did not show any long-term effects. The

ordinary practitioner clearly would not expect good results and would not predict long-term immunity extending to six months in the absence of the art-recognized two-shot approach to vaccination. The authors effectively teach away from the claimed method in which there is single administration of the claimed vaccine to effectively vaccinate the pig.

The adjuvant formulation taught by Byars *et al.* is not even a mere mixture of metabolizable oil and a polyoxyethylene-polypropylene block copolymer. For weak antigens, Byars *et al.* expressly teach an adjuvant formulation that includes a mixture of PLURONIC L121 and squalene or squalane with muramyl dipeptides (MDP). The authors indicate on page 226 that while the formulation without added MDP does induce good secondary antibody titres in combination with the egg albumin, after a boost, the inclusion of (Thr¹]-MDP in the primary immunization gives superior results. The authors never propose administering their adjuvant formulation without MDP in the primary immunization, and never recommend a single administration of vaccine to elicit protective immunity.

The secondary reference of Liem *et al.* does not provide the missing link to the two primary references to enable the ordinary practitioner to be able to arrive at the claimed invention. Liem *et al.* concern a killed whole cell culture of the *F. necrophorum* bacteria that is cultured for at least 10 hours to improve its antigenicity. The exemplification of the invention of Liem *et al.* shows that their vaccine is given by the conventional two-shot process, first at day 0 or day 1 and then again at day 21 (see paragraphs (0043) and (0052)). The studies stop at 50 days. Although the reference implies numerous adjuvants could be used with the *F. necrophorum* bacteria (paragraph (00301)), the examples only show an oil-based adjuvant called SuprImm Oil. The bare disclosure of many different adjuvants that may be employed in a formulation containing *F. necrophotum* bacteria is very limited in its teachings. The long generic list of possible choices does not describe or propose a specific mixture of metabolizable oil and a polyoxyethylene-polypropylene block copolymer, nor does it suggest that such a mixture should be combined with the *Mycoplasma hyopneumoniae* bacterin of Petersen *et al.*, let alone imply that the unique formulation with polyacrylic acid polymers would give long-term immunity after a single administration. The combined art fails to render the claimed invention *prima facie* obvious. There is no description or suggestion in any of the cited references that single administration of the *Mycoplasma hyopneumoniae* bacterin when

formulated according to the present invention could be successful at achieving effective immunity for six months. It is clear that there is no teaching in the combined art to suggest or motivate the ordinary practitioner to produce the claim-recited vaccine of the present application and practice the claimed method.

With regard to the rejection of claim 17 under 35 U.S.C. 103(a) as being unpatentable over Petersen *et al.* as modified by Byars *et al.* and Liem *et al.* as applied to claim 10 and further in view of Burkhardt *et al.* and Potter *et al.* , Applicants submit the following arguments. Applicants contend that: (a) The combination of Petersen *et al.* as modified by Byars *et al.* and Liem *et al.* does not teach or suggest the mixture of metabolizable oil and a polyoxyethylene-polypropylene block copolymer in combination with polyacrylic acid polymers and the *Mycoplasma hyopneumoniae* bacterin; (b) The combined art does not describe or infer that the vaccine formulation made according to the present invention should be given as a single vaccination or would be effective in one dose; (c) The ordinary practitioner would not expect or be able to predict the long-term, six-month immunity achieved from the novel vaccine of this invention based on the combined art of Petersen *et al.* as modified by Byars *et al.* and Liem *et al.* (d) The tertiary references do not supply the missing teachings needed in order to arrive at the method of claim 17. Burkhardt *et al.* concern a cell-free extract preparation of *Haemophilus parasuis*. Patentees indicate that the *H. parasuis* may be combined with a broad variety of adjuvants (column 3, lines 12-19) and may be formulated into multivalent vaccines that can contain *Mycoplasma hyopneumoniae* (column 3, lines 38-47). However, they do not illustrate any multivalent vaccine formulations and only show monovalent vaccine formulations containing Diluvac Forte adjuvant. The patentees expressly teach that the use of adjuvants is not necessary to provide immunogenic activity to their composition (column 3, lines 17-19). They explicitly further instruct that the vaccine is most effective if administered in a series of at least two doses separated by two or three week intervals (column 3, lines 22-24) plus exemplify vaccinating the pigs at 3 and 6 weeks (Example 5, column 6, lines 29-32). Their studies only went to 9 weeks. It is clear that Burkhardt *et al.* do not provide any motivation to the ordinary practitioner to do what Applicants have done. The patent does not suggest the advantage of employing the mixture of metabolizable oil and a polyoxyethylene-polypropylene block copolymer in combination with polyacrylic acid polymers and, in no uncertain terms,

effectively teaches away from the single administration of the multivalent vaccine. Applicants' excellent results are clearly unanticipated in light of the teachings of Burkhardt *et al.* Reliance on Potter *et al.* is not justified in the Examiner's rejection of claim 17. Potter *et al.* relate to subunit vaccines containing *H. somnus* outer membrane protein extracts enriched with iron-regulated proteins. Because this reference does not teach or suggest any of the limitations recited in claim 17, Potter *et al.* should be removed as a cited reference. Even if the teachings were combined, the ordinary practitioner would still not arrive at the multivalent vaccine or its use as recited in claim 17 and would not achieve what the inventors have done. There is no reason taught in the art to include the mixture of metabolizable oil and a polyoxyethylene-polypropylene block copolymer with polyacrylic acid polymers and the *Mycoplasma hyopneumoniae* bacterin; to eliminate the MDP taught as essential for immunity by Byars *et al.*; and not to administer the vaccine by the conventional two-step process. There is no reasonable expectation of success in a single administration of the vaccine prepared according to the teachings in the present application, and certainly no expectation at all of long-term immunity to six months. The *prima facie* case of obviousness has not been established in light of the unexpected and significant results exemplified by the vaccine of the present invention.

Applicants' arguments have been carefully considered, but are not persuasive. As set forth previously, the Office has established a *prima facie* case of obviousness. First, the instant claims do not recite that the single administration of the recited vaccine composition confers protection against *M. hyopneumoniae* for four months following the vaccination. Claims, as presented currently, do not require that the claimed method provides long-term immunity to full six months after the single dose administration without the booster shot. The age of porcine animals is not a claim limitation that is required to be met. The limitation 'porcine animal' encompasses both young and old animals. That Petersen's method of protecting porcine animals by administering a single dose of the *M. hyopneumoniae* bacterin as disclosed in Petersen's Example 2 does in fact reduce the number of times that the porcine animals are vaccinated by alleviating handling stress, reducing vaccination time and decreasing labor time is implicit from the teachings of Petersen *et al.*

With regard to Applicants' extensive discussion of Example 3 of Petersen *et al.*, it should be noted that Petersen's Example 3 was not cited in the Office Action as being relevant to the instant

claims. Instead, it was Petersen's Example 2 which was set forth in the Office Action, since Petersen's Example 2 taught a method of protecting a porcine animal by administering a single dose of *M. hyopneumoniae* bacterin contained in PBS and CARBOPOL. See paragraph 18 of the Office Action mailed 01/06/05. Therefore, Applicants' arguments on Petersen's Example 3 are not relevant to the art rejection of record. Contrary to Applicants' assertion, instant claims as presented currently, do not require the claimed method to induce 'long-term immunity extending to six months' or 'long lasting protection'. Petersen *et al.* did not just imply that one dose of the bacterin can be injected into swine at lines 12-16 of page 12. Instead, Petersen *et al.* at Example 2 did establish a meaningful protection in vaccinated pigs after a single vaccination. Addition of another art-known adjuvant or adjuvant mixture such as the one taught by Byars *et al.* to the single dose CARBOPOL-containing *M. hyopneumoniae* bacterin that already existed in the art would have been well within the realm of routine experimentation. One of ordinary skill in the art would expect such mixture to improve the protective efficacy of the *M. hyopneumoniae* bacterin vaccine in an additive or cumulative manner. Such addition of Byars' adjuvant mixture to Petersen's CARBOPOL-containing *M. hyopneumoniae* bacterin is expected to further improve the protective efficacy of Petersen's bacterin and would have been obvious to one of ordinary skill in the art, given that the use of combination of adjuvants with *M. hyopneumoniae* vaccines or antigens was known in the state of the art at the time of the invention. For instance, Keich *et al.* (US 6,846,477, filed 07/02/01) disclosed the use of 'combinations of adjuvants' including CARBOPOL, PLURONIC and vegetable or mineral oils with *M. hyopneumoniae* vaccines (see last full paragraph in column 6). Keich *et al.* show that single-dose inactivated *M. hyopneumoniae* whole cell vaccines capable of conferring protection to pigs even without the use of an adjuvant mixture were available in the art at the time of the invention. One such vaccine is the commercially available RESPIFEND vaccine from Fort Dodge, American Home Products (see lines 52-60 in column 4 of Keich *et al.*), i.e., the same vaccine described by Applicants as Petersen's RespiFend by FDAH on page 4 of their response filed 04/06/05. This independent evidence from the art provides the additional *prima facie* evidence and establishes that Petersen's bacterin does provide protection after administration of a single dose.

To some extent, Applicants argue as though the reference of Byars *et al.* or Liem *et al.* is applied as an anticipatory reference under 35 U.S.C § 102. Applicants are reminded that the

reference of Byars *et al.* is cited as a secondary reference under 35 U.S.C § 103 to document that the use of a mixture of squalane and PLURONIC L121 with inactivated vaccines and veterinary vaccines was expressly suggested in the art at the time of the invention. Contrary to Applicants' assertion, Byars *et al.* do not teach away from the instant invention. Byars *et al.* expressly taught that their adjuvant mixture formulation, comprising PLURONIC L121 and squalane, will be 'useful for both human and *veterinary* vaccines', and that it was 'found to be effective with several antigens' and 'in several species'. See abstract of Byars *et al.* One of skill in the art would readily understand that Petersen's CARBOPOL-containing *M. hyopneumoniae* bacterin is a *veterinary* vaccine. Byars *et al.* expressly taught that their adjuvant mixture formulation 'is not restricted to use with soluble antigens', but is usable with inactivated vaccines. One of skill in the art would readily understand that Petersen's CARBOPOL-containing *M. hyopneumoniae* bacterin is an *inactivated* vaccine. Nowhere do Byars *et al.* limit the use of their adjuvant mixture formulation for use with 'a weak antigen'. Furthermore, Byars *et al.* taught that their adjuvant mixture formulation 'increases both cell-mediated and humoral immunity and is free of significant side effects encountered with other adjuvants or vehicles'. See abstract of Byars *et al.* Given Petersen's express disclosure at the end of page 32 that cell-mediated immunity and antibodies are important in immunoprotection against infection by *M. hyopneumoniae*, one of ordinary skill in the art would have been motivated to add Byars' adjuvant mixture formulation comprising squalane and PLURONIC L121 to Petersen's CARBOPOL-containing *M. hyopneumoniae* bacterin single dose veterinary vaccine for the purpose of further enhancing both types of immune responses to Petersen's CARBOPOL-containing *M. hyopneumoniae* bacterin, since Byars *et al.* specifically taught that their adjuvant mixture formulation: a) is 'useful for both human and *veterinary* vaccines'; (b) is 'found to be effective with several antigens' and 'in several species'; (c) 'is not restricted to use with soluble antigens', but is usable with 'inactivated' vaccines; and (d) 'increases both cell-mediated and humoral immunity and is free of significant side effects encountered with other adjuvants or vehicles'. Contrary to Applicants' assertion, nowhere in their reference Byars *et al.* teach against using their adjuvant mixture formulation with a *veterinary* vaccine or an inactivated bacterial vaccine. With regard to Applicants' remarks on the presence of MDP in Byars' adjuvant mixture, it must be noted that the

open claim limitation 'adjuvant mixture comprising' in claim 10 does not exclude MDP or any other element from being present in the adjuvant mixture.

Contrary to Applicants' assertion, the adjuvant taught by Byars *et al.* comprises a mixture of a metabolizable oil (5% squalane) and a polyoxyethylene-polyoxypropylene block polymer (2.5% PLURONIC L121). Byars' PLURONIC L121 is the same as the PLURONIC L121 recited as being a preferred polyoxyethylene-polyoxypropylene block polymer in the instant invention. See second full paragraph on page 5 of Applicants' specification. Byars' squalane is the same squalane that is recited in instant claim 16 as a 'metabolizable oil'. Byars *et al.* or Liem *et al.* do not have to teach a polyacrylic acid polymer or CARBOPOL, because the single dose *M. hyopneumoniae* bacterin vaccine of Petersen *et al.* already contains CARBOPOL. There is no teaching or inference in Example 2 of Petersen *et al.* that a second booster shot is required.

As is clear from paragraph 18 of the Office Action mailed 01/06/05, Liem *et al.* was applied in the rejection to document the routine and conventional practice of using a combination or mixture of art known adjuvants, such as, squalene or squalane and PLURONIC along with known bacterial vaccines. Liem *et al.* taught the preferable embodiment of using a combination adjuvant comprising oils, polymers, and block co-polymers. See section [0030]. Applicants' arguments on Liem's *F. necrophorum* are irrelevant to the rejection of record.

Contrary to Applicants' argument, the PBS- and CARBOPOL-containing *M. hyopneumoniae* bacterin of Petersen *et al.* conferred protection after administration of a single dose (see Example 2). At the time of the effective filing date of the instant application, single-dose *M. hyopneumoniae* bacterins that conferred protection to pigs were commercially available. For instance, Keich *et al.* (US 6,846,477, filed 07/02/01) disclosed a method of treating or preventing a *Mycoplasma hyopneumoniae* infection in a pig at from about 3 to about 10 days of age comprising administering an effective amount of a single dose of a *Mycoplasma hyopneumoniae* vaccine comprising an inactivated *Mycoplasma hyopneumoniae* whole cell preparation (see claims). Keich's one dose *M. hyopneumoniae* bacterin was used in a method of treating or preventing *Mycoplasma hyopneumoniae* infection in a pig without an adjuvant (see claim 2 of Keich *et al.*). Keich *et al.* also taught that RESPIFEND, HYORESP, PROSYSTEM M, INGLEVAC M, RESPISURE, or STELLAMMUNE MYCOPLASMA are the other *M. hyopneumoniae* bacterins suitable for use in

their method (see lines 52-60 in column 4 of Keich *et al.*). See also section 'Relevant Prior Art' below.

In response to Applicants' arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In response to Applicant's argument that the references fail to show certain features of Applicants' invention, such as duration of protection and the age of the porcine animal, it is noted that the features upon which Applicants rely are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

In sum, Applicants appear to argue that the combination of references fails because the prior art does not have anticipatory references regarding all elements of the invention. The argument is not persuasive. It should be noted that what would reasonably have been known and used by one of ordinary skill in the art need not be explicitly taught. See *In re Nilssen*, 851 F.2d 1401, 7 USPQ2d 1500 (Fed. Cir. 1988). The test of obviousness is not express suggestion of the claimed invention in any and all of the references, but rather what the references taken collectively would reasonably have suggested to those of ordinary skill in the art presumed to be familiar with them. *In re Keller*, 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981). In the instant case, there is express suggestion provided by Paradiso *et al.* to mix group B meningococcal outer membrane vesicles with a group C and/or A conjugate. Obviousness does not require absolute predictability, (see *In re Lamberti*, 192 USPQ 278), but only a reasonable expectation of success (see *In re O'Farrell*, 7 USPQ 2d 1673, Fed. Cir. 1988), which has been established. The rejection stands.

Double Patenting

9) The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the 'right to exclude' granted by a patent and to prevent possible

harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970) and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 C.F.R. 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 C.F.R. 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 C.F.R. 3.73(b).

10) Claims 10-12 and 14-17 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 14-18 of the co-pending application, SN 10/150,597. Although the conflicting claims are not identical, they are not patentably distinct from each other because the method claimed in the co-pending application is encompassed within the scope of the instant claims.

Rejection(s) under 35 U.S.C. § 112, First Paragraph (New Matter)

11) Claim 10 and those dependent therefrom are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 10 includes the limitation: ‘nasal’ administration. However, there is no descriptive support in the specification, as originally filed for the above-identified new limitation. Therefore, the above-identified limitations in the claims are considered to be new matter. *In re Rasmussen*, 650 F.2d 1212 (CCPA, 1981). New matter includes not only the addition of wholly unsupported subject matter but also, adding specific percentages or compounds after a broader original disclosure, or even omission of a step from a method. See M.P.E.P 608.04 to 608.04(c).

Applicants are respectfully requested to remove the new matter from the claim(s), or invited to point to specific pages and line numbers in the originally filed specification where support for such a recitation can be found.

Rejection(s) under 35 U.S.C. § 112, Second Paragraph

12) Claims 10-12 and 14-17 are rejected under 35 U.S.C § 112, second paragraph, as being indefinite, for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

(a) Claim 10 is vague and confusing in the limitation: ‘polyoxyethylene-polypropylene block copolymer’, which limitation is inconsistent with the limitation ‘polyoxyethylene-polyoxypropylene block copolymer’ recited at line 20 on page 5 of the specification. Which limitation represents the accurate limitation is not clear.

(b) Claim 10 is indefinite, confusing and/or inconsistent in the limitations: ‘protecting against disease caused by *Mycoplasma hyopneumoniae*’ and ‘protective immunity from *Mycoplasma hyopneumoniae* infection’. It is unclear how a ‘disease caused by *Mycoplasma hyopneumoniae*’ differs in scope from ‘*Mycoplasma hyopneumoniae* infection’.

(c) Claim 15 contains the trademark/trade name ‘CARBOPOL’. Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to identify/describe CARBOPOL and, accordingly, the identification/description is indefinite.

(d) Claim 17 is indefinite and incorrect in the limitation: ‘claims 10-16’, because claim 13 encompassed in the limitation has been canceled.

(e) Claims 11, 12 and 14-17, which depend from claim 10, are also rejected as being indefinite, because of the vagueness or indefiniteness identified above in the base claim.

Rejection(s) under 35 U.S.C § 103

13) Claims 10-12 are rejected under 35 U.S.C § 103(a) as being unpatentable over Petersen *et al.* (WO 92/03157, already of record) and Byars *et al.* (*Vaccine* 5: 223-228, 1987, already of record) in view of Liem *et al.* (US 20020114817, filed 09/29/1999 – already of record).

The reference of Liem *et al.* is used in this rejection because it qualifies as prior art under subsection (e) of 35 U.S.C. § 102 and accordingly is not disqualified under U.S.C. 103(a).

The transitional phase ‘comprising’ defines the scope of a claim with respect to what unrecited additional components or steps, if any, are excluded from the scope of the claim. The transitional term ‘comprising’ is synonymous with ‘including’, ‘containing’, or ‘characterized by’ is inclusive or open-ended and does not exclude additional, unrecited elements or method steps. *Moleculon Research Corp. v. CBS, Inc.*, 793 F.2d 1261, 229 USPQ 805 (Fed. Cir. 1986); *In re Baxter*, 656 F.2d 679, 686, 210 USPQ 795, 803 (CCPA 1981); and *Ex parte Davis*, 80 USPQ 448, 450 (Bd. App. 1948) (‘comprising’ leaves ‘the claim open for the inclusion of unspecified ingredients even in major amounts’).

Petersen *et al.* disclosed a method of protecting pigs against *M. hyopneumoniae* infection comprising administering to said pigs intramuscularly ‘a 2-ml dose’ (i.e., a single dose of an immunizing amount) of a *M. hyopneumoniae* bacterin contained in PBS (i.e., a pharmaceutically acceptable carrier) and CARBAPOL (i.e., polyacrylic acid polymer). The single 2-ml dose contained 5×10^{10} CCU. The method reduced the mean percent lesion score by approximately 60% and protected the vaccinated pigs against *Mycoplasma hyopneumoniae* challenge infection. See Example 2; see second and third full paragraphs on page 30; third and fourth full paragraphs on page 32; paragraph bridging pages 32 and 33; claims 20-23; and Table 3. The effective amount to immunize a swine is at least about 10^9 *M. hyopneumoniae* DNA cell equivalents per milliliter of bacterin (see last half of page 8). The vaccine is also administered through various other routes (see page 12). The vaccine comprises one or more of other antigenic substances capable of inducing a protective immune response against other disease-causing agents (see third full paragraph on page 13). Petersen *et al.* further taught that the importance of cell mediated

immunity and antibodies in immunoprotection against infection by *M. hyopneumoniae* (see last paragraph on page 32).

Petersen *et al.* differ from the instant invention in not having a metabolizable oil and a polyoxyethylene-polypropylene block copolymer admixed with their CARBOPOL adjuvant in the vaccine used.

However, the use of an adjuvant mixture in a veterinary vaccine wherein the adjuvant mixture contains a metabolizable oil comprising trepane hydrocarbon, such as, squalene or squalane, and a polyoxyethylene-polypropylene block copolymer, such as, PLURONIC L121 was well known in the art at the time of the invention. For instance, Byars *et al.* taught adding a safe, efficacious, non-allergenic, metabolizable and easily prepared adjuvant, SAF-1, which comprises 10% squalene or squalane, **plus** 2.5% v/v PLURONIC L121 to vaccines for eliciting both humoral and cell-mediated immunity. Byars *et al.* taught that this new adjuvant formulation avoids the difficulties encountered with Freund's adjuvant, such as, non-approval for continued human use and formation of sterile abscesses; and also the carcinogenic nature of Arlacel A (see pages 223 and 224). Byars *et al.* expressly recommended the use of their adjuvant formulation with a wide variety of antigens in human and *veterinary* vaccines (see page 223 and 227). Byars *et al.* taught that the adjuvant formulation is not only used with soluble antigens but also with *inactivated* vaccines (see page 226).

Liem *et al.* showed the routine and conventional practice of using a combination or mixture of art known adjuvants, such as, squalene or squalane and Pluronic along with known bacterial vaccines. Liem *et al.* taught the preferable embodiment of using a combination adjuvant comprising oils, polymers, and block co-polymers. See section [0030].

Given the routine and conventional mixing of several art-known adjuvants including oils, polymers and block co-polymers in an art-known vaccine as taught by Liem *et al.*, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to add Byar's SAF1 adjuvant formulation comprising squalene or squalane and PLURONIC L121 mixture to the CARBOPOL-containing single dose *M. hyopneumoniae* bacterin vaccine used in Petersen's method to produce the instant invention with a reasonable expectation of success,

because Byars *et al.* expressly taught that their safe, efficacious, non-allergenic, metabolizable, and easily prepared SAF-1 adjuvant formulation is useful in both veterinary and human vaccines with a wide variety of antigens. Given Petersen's express teaching about the importance of antibodies and cell mediated immunity in immunoprotection against *M. hyopneumoniae* infection, one of skill in the art would have been motivated to produce the instant invention for the expected benefit of further enhancing the immunogenicity of Petersen's vaccine in Petersen's method of protection by promoting the elicitation of both humoral and cell-mediated immunity to Petersen's *M. hyopneumoniae* bacterin while avoiding safety related difficulties such as formation of sterile abscesses and carcinogenicity associated with other art known adjuvants as taught by Byars *et al.*

Claims 10-12 are *prima facie* obvious over the prior art of record.

14) Claim 17 is rejected under 35 U.S.C § 103(a) as being unpatentable over Petersen *et al.* (WO 92/03157) as modified by Byars *et al.* (*Vaccine* 5: 223-228, 1987) and Liem *et al.* (US 20020114817, filed 09/29/1999) as applied to claim 10 above, and further in view of Frantz *et al.* (US 5,695,769) and Pijoan (US 6,585,981).

The reference of Pijaon is used in this rejection because it qualifies as prior art under subsection (e) of 35 U.S.C. § 102 and accordingly is not disqualified under U.S.C. 103(a).

The teachings of Petersen *et al.* as modified by Byars *et al.* and Liem *et al.* are disclosed above, which do not teach co-administering the *M. hyopneumoniae* bacterin preparation with an additional bacterin such as *Haemophilus parasuis* bacterin as recited in claim 17.

However, addition of inactivated bacterins of other veterinary pathogens to inactivated *Mycoplasma hyopneumoniae* was already known in the art at the time of the invention. For example, Frantz *et al.* disclosed the routine and conventional practice in the art of vaccines of combining inactivated *Mycoplasma hyopneumoniae* with other inactivated microorganisms, such as, *B. bronchiseptica* and *P. multocida* (see lines 19-25 in column 19). Frantz *et al.* taught the use of appropriate inactivated pathogens in combined vaccines based on the animal to be vaccinated, the disease for which protection is desired, and other related factors (see lines 37-49 in column 22).

Pijoan expressly taught that *M. hyopneumoniae* bacterin may be used in combination

with other vaccines for convenience or enhanced results, and that the combination vaccine preferably provides protection against plural infections. Pijoan expressly taught that of particular interest is the combination of *M. hyopneumoniae* and *Bordetella bronchiseptica* and *Pasteurella multocida*, because all these cause significant disease in swine. Pijoan further taught that these other vaccines may be inactivated by entirely different means (see paragraph bridging columns 5 and 6).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine Frantz's inactivated bacterin of *B. bronchiseptica* and/or *P. multocida* to Petersen's single dose *M. hyopneumoniae* bacterin for use in Petersen's method as modified by Byars *et al.* and Liem *et al.* to produce the instant invention, with a reasonable expectation of success because Pijoan expressly taught that *M. hyopneumoniae* bacterin may be used in combination with other vaccines for convenience or enhanced results. Given Petersen's express teaching that their vaccine can comprise one or more of other antigenic substances capable of inducing a protective immune response against other disease-causing agents, given Pijoan's express teaching that *M. hyopneumoniae* bacterin may be used in combination with other vaccines including *Bordetella bronchiseptica* and *Pasteurella multocida*, and given Pijoan's express teaching that *M. hyopneumoniae*, *B. bronchiseptica*, and *P. multocida* are three bacterial pathogens that cause significant disease in swine, one of skill in the art would have been motivated to produce the instant invention for the expected benefit of convenience, enhanced results, and providing protection against plural porcine infections as taught by Pijoan.

Claim 17 is *prima facie* obvious over the prior art of record.

Relevant Prior Art

15) The relevant prior art made of record and not currently relied upon in any of the rejections is considered pertinent to Applicants' disclosure. The following references document that single dose *Mycoplasma hyopneumoniae* vaccines conferred protection even without the use Applicants' adjuvant mixture.

- Keich *et al.* (US 6,846,477, issued 01/25/05) discloses a method of treating or preventing a *Mycoplasma hyopneumoniae* infection in a pig at from about 3 to about 10 days of

age comprising administering an effective amount of a single dose of a *Mycoplasma hyopneumoniae* vaccine comprising an inactivated *Mycoplasma hyopneumoniae* whole cell preparation (see claims).

- Martinon *et al.* (In: Proceedings of the 15th IPVS Congress. (Ed) Stanley Done *et al.* Birmingham, England, 5-9 July 1998, page 284) disclosed the efficacy of a 'one shot' *Mycoplasma hyopneumoniae* Hyoresp vaccine in pigs at 10 weeks, 11 weeks and 10-12 weeks of age. Under all conditions tested in the studies, the 'one shot' regimen provided significant protection (see page 284).

- Reynaud *et al.* (In: Proceedings of the 15th IPVS Congress. (Ed) Stanley Done *et al.* Birmingham, England, 5-9 July 1998, page 150) disclosed the results of a clinical field trial of one injection- *Mycoplasma hyopneumoniae* Hyoresp vaccine in piglets (see page 150).

- Charlier *et al.* (In: Proceedings of the 16th IPVS Congress. (Ed) Cargill *et al.* Melbourne, Australia, 17-20 September 2000, page 501) disclosed the comparative efficacy of one injection of STELLAMMUNE *Mycoplasma* and HYORESP *Mycoplasma hyopneumoniae* vaccine in pigs at about 10 weeks of age (see page 501).

- Pijoan (WO 02/10343 A2, filed 07/27/00) disclosed a method of protecting swine against *Mycoplasma hyopneumoniae* infection by administering a single intramuscular dose of a whole cell *Mycoplasma hyopneumoniae* vaccine or bacterin (see claims 8-17; Example 2; and line 26 on page 10). Furthermore, Pijoan expressly taught that *Mycoplasma hyopneumoniae* vaccine or bacterin may be used in combination with other vaccines for convenience, enhanced results, or for providing protection against plural infections. Pijaon taught that other vaccines may be inactivated by entirely different means. Pijoan further taught that, of particular interest is the combination of *Mycoplasma hyopneumoniae* and *Bordetella bronchiseptica* and *Pasteurella multocida* because all three cause significant disease in swine (see last paragraph on page 8).

Remarks

16) Claims 10-12 and 14-17 stand rejected.

17) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center, which receives transmissions 24 hours a day and 7 days a week. The transmission of such papers by facsimile must conform with

the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The Fax number for submission of amendments, responses or papers is (571) 273-8300.

18) Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAG or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.Mov>. Should you have questions on access to the Private PAA system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

19) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (571) 272-0854. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (571) 272-0864.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

August, 2005


S. DEVI, PH.D.
PRIMARY EXAMINER